B. Summary of the Outstanding Office Action

In the Office Action of 13 June 2001, claim 50 was rejected under 35 USC § 112, first paragraph, with the assertion that the language "the Euclidean representation is a two-dimensional plot of a first reaction value on the x-axis and a second reaction value on the y-axis" constituted new matter. It was asserted that the specification of the application did not discuss any plots associated with the Euclidean representation and that the specification gave no basis for a two-dimensional plot.

Claims 48 through 68 inclusive were rejected in the outstanding Office Action under 35 USC § 112, second paragraph, with the assertion that the phrase "Euclidean representation" was vague and indefinite.

In the Office Action of 13 June 2001, claims 48 through 55 inclusive and 69 through 71 inclusive were rejected under 35 USC § 102(a) as unpatentable over a publication by Kimpton *et al.* in *PCR Methods and Applications*, volume 3, pages 13 through 22 (August 1993) ("the Kimpton *et al.* publication"). It was asserted that the Kimpton *et al.* publication disclosed at page 14 a method of determining the genotype at a locus within genetic material obtained by polymerase chain reaction ("PCR") amplification. With citations to pages 15 through 17 and Figure 1 of the Kimpton *et al.* publication, it was asserted that the method of the publication included the steps of reacting the material at the locus to produce a first reaction value indicative of the presence of the given allele at the locus; forming a data set including the first reaction

value; establishing a plurality of distribution sets of probability distributions where hypothetic reaction values were associated with each genotype of interest at the locus; applying the first reaction value to each pertinent probability of each genotype at the locus; and determining the genotype based on the data obtained from the proceeding step. In connection with the rejection under 35 USC § 102(a), it was asserted that the Kimpton *et al.* publication disclosed reacting material at multiple loci and considered multiple alleles in the probability distributions. It was asserted that the Kimpton *et al.* publication disclosed the use of multiple data points derived from multiple runs of automated apparatus. It was asserted that the Kimpton *et al.* publication disclosed the selection of loci for their discrimination ability and disclosed that the locus could be dinucleotide or tetranucleotide repeats.

In the outstanding Office Action, claims 48 through 55 inclusive and 60 through 69 inclusive were rejected under 35 USC § 103(a) as unpatentable over the Kimpton *et al.* publication in view of a publication by Clark in *Mol. Biol. Evol.*, volume 7, pages 111 through 122 (March 1990) ("The Clark publication"). It was admitted in the outstanding Office Action that the Kimpton *et al.* publication did not disclose modification of data to iteratively improve an assay. It was asserted that the Clark publication disclosed a method of resolving ambiguities by performing an iterative cascade of improvements on data points. It was asserted that the method of the Clark *et al.* publication was applied to restriction site polymorphisms. With a reference to a passage in the abstract of the Clark publication which asserted that the algorithm of the publication applied to the problem of inferring haplotype frequencies of closely linked restriction

site polymorphisms, it was asserted that an ordinary practitioner would have been motivated to apply the conceptual idea of iterative data processing of the Clark publication in the genotyping method of the Kimpton *et al.* publication in order to extract as close to the entirety of the allelic sequences as possible. It was asserted further that an ordinary practitioner would have recognized that the method could be performed using any link marker, including single nucleotide polymorphisms such as the restriction site polymorphisms assertedly disclosed in the Clark publication.

Claims 48 through 69 inclusive were rejected under 35 USC § 103(a) in the Office Action of 13 June 2001 as unpatentable over the Kimpton *et al.* publication in view of Clark publication and further in view of published International Patent Application WO 92/15712 to Goelet *et al.* ("the Goelet *et al.* '712 published international application"). It was admitted in the outstanding Office Action that the Kimpton *et al.* publication even in view of the Clark publication did not teach genetic bit analysis. It was asserted that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of the hypothetical combination of the Kimpton *et al.* publication in view of the Clark publication with the use of genetic bit analysis or allele specific amplification to develop the data in view of the Goelet *et al.* '712 international published application. It was asserted that an ordinary practitioner would have been motivated to substitute an assertedly equivalent genetic bit analysis method for PCR assertedly in order to minimize the need for gel electrophoresis and enhance the

automatability of the process as assertedly motivated by the Goelet *et al.* international published application assertedly in order to speed analysis and minimize cost.

Claims 48 through 56 inclusive 58, and 60 through 69 inclusive were rejected in the outstanding Office Action under 35 USC § 103(a) as unpatentable under the Kimpton *et al.* publication in view of the Clark publication and further in view of United States patent No. 5,516,663 to Backman *et al.* ("the Backman *et al.* '663 patent"). It was admitted in the Office Action that the Kimpton *et al.* publication even in view of the Clark *et al.* publication did not disclose the use of a ligation chain reaction. It was asserted that the Backman *et al.* '633 patent disclosed a method of ligation chain reaction. It was asserted that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of the hypothetical combination of the Kimpton *et al.* publication in view of the Clark publication with the use of a ligation chain reaction as assertedly disclosed in the Backman *et al.* '663 patent. A passage at column 2, lines 8 through 10 of the Backman *et al.* '663 patent was cited in this connection. It was asserted that an ordinary practitioner would have been motivated to substitute the ligation chain reaction for an assertedly equivalent amplification method of polymerase chain reaction with the asserted motivation that the ligation chain reaction assertedly could detect small numbers of target molecules and assertedly because ligation chain reaction was a known equivalent amplification assay to the polymerase chain reaction disclosed in the Kimpton *et al.* publication.

C. Summary of the Present Amendments
And Request for Reconsideration

In the present response claims 48 through 50 and 55 have been canceled without prejudice. The applicants expressly reserve the right to prosecute claims directed to the subject matter of the cancelled claims in one or more continuation, divisional, or continuing application.

New claims 72 through 74 inclusive have been added to the present response. The new claims find support in the application as originally filed, for example, at page 2, line 11 through page 3, line 20 and page 12, line 5 through page 16, line 12. It is submitted that new claims 72 through 74 inclusive do not constitute new matter.

Dependent claims 51, 52, 56, 58, 60, and 62 through 68 were amended to bring dependencies into accord with the new claims.

Reconsideration of the subject application as amended above in light of the comments below is respectfully requested.

D. The Rejection Under U.S.C. § 112, First Paragraph

It is submitted that the language in claim 50 concerning a Euclidian representation as a two-dimensional plot of a first reaction value on the x axis and a second reaction value on the y axis finds support in the application as filed – if not *in haec verba*, then as the application would

have been understood by a person of even only ordinary skill in the art – at, for example, page 12, line 21 through page 13, line 12. It is submitted therefore that the rejection under 35 U.S.C. § 112, first paragraph, with reference to the language in claim 50 was without justification.

However, in order to expedite prosecution of the subject application, claim 50 has been cancelled without prejudice. The claims as amended in the present reply do not include the language cited in the rejection under the first paragraph of 35 U.S.C. § 112 in the outstanding Office Action, and therefore the rejection has been rendered moot. It is submitted the claims of the application as amended meet the standards of 35 U.S.C. § 112, first paragraph.

E. The Rejection Under 35 U.S.C. § 112, Second Paragraph

It is submitted that persons of even ordinary skill in the art, as of the effective filing of the subject application, would have understood the phrase "Euclidian representation," as used in claims 48 and 50, and, by reference, claims 49 and 51 through 68 inclusive dependent upon claims 48 or 50 directly or indirectly, particularly in light of the disclosure of the application as filed at page 12, line 21 through page 13, line 12. Consequently, it is submitted that the rejection under 35 U.S.C. § 112, second paragraph, with the assertion that the phrase "Euclidian representation" was vague and indefinite, was unwarranted.

However, in order to expedite prosecution of the subject application, claims 48 and 50 have been cancelled without prejudice in the present reply. New independent claim 72 and dependent claims 73, 74, 51 through 54 inclusive, and 56 through 68 inclusive do not employ the phrase "Euclidian representation." Consequently, the rejection under 35 U.S.C. § 112, second paragraph, in the outstanding Office Action has been rendered moot. It is submitted that the claims of the application as amended meet the standards of 35 U.S.C. § 112, second paragraph.

F. The Rejection Under 35 U.S.C. § 102(a)

The Kimpton *et al.* publication disclosed automated DNA profiling, based on detection of amplified of tri-, tetra-, and pentanucleotide short-tandem-repeat ("STR") loci by electrophoresis on denaturing polyacrylamide sequencing gels using automated fluorescence-based technology. According to the abstract of the Kimpton *et al.* publication, the system of the publication used an internal size standard in each sample to permit the short tandem repeat products amplified by PCR to be sized automatically. Three multiplex short-tandem-repeat systems containing a total of fourteen different loci were used, with different fluorescent markers used for loci which had overlapping allele size ranges.

According to column 3, lines 20 through 29 of page 13 of the Kimpton *et al.* publication, dinucleotide short-tandem repeats exhibited "slippage" during amplification which resulted in artifactual "stutter bands." The publication disclosed that such stutter bands made unambiguous allele designation difficult. It was stated that tri- and tetrameric repeats had a wider allele

spacing and appeared to be significantly less prone to slippage, and therefore more suitable for the technique of the publication.

According to column 1, lines 4 through 15 of page 16 of the Kimpton *et al.* publication, 14 three to five-base-pair short-tandem-repeat loci were selected for evaluation based on their predicted discrimination power. Amplification products of the short-tandem-repeat loci were tagged by the attachment of a fluorescent dye molecule to one of each pair of the loci-specific amplification primers. During electrophoresis on denaturing polyacrylamide gels, amplified products were detected by laser scanning. According to column 1, lines 17 through 34 of page 15 of the publication, fragment sizes after eight hours of electrophoresis on an automated DNA sequencer were determined using software employing a method of second order regression to establish a curve of best fit for the internal standard in each lane. According to page 16, column 2, line 16 through column 3, line 14, two of the short-tandem repeat loci selected displayed a number of allele bands which differed by one base pair and two base pairs. It was noted that although such differences could be resolved on the polyacrylamide gels, the consistency of automatic sizing between gels was not sufficient to allow precise allele designation using those loci. A direct comparison of computer generated band sizes to those of an alleic ladder control run on the same gel was required in order to assign the two loci in question.

In contrast, new claim 72 of the subject application as amended is directed to a method of determining both genotype and confidence scores at a genetic locus for a plurality of samples of

genetic material, where the samples have been prepared under comparable conditions. The method includes the step of assembling reaction-value data points for the samples. Each reaction-value data point is specified to correspond to a respective one of the samples and to include at least one reaction value. The method of new claim 72 further includes the step of determining an initial conditional probability for each reaction-value data point for each genotype and computing a conditional probability of each genotype for each reaction-value data point. The method of new claim 72 finally includes the step of determining the genotype and confidence score for each reaction-value data point, thus determining the genotype and confidence score at the genetic locus for each sample.

For the reasons set forth above, it is submitted that the automated DNA profiling method of the Kimpton *et al.* publication would have neither disclosed nor in any way suggested the method of determining the genotype and confidence scores at a genetic locus of new claim 72 of the subject application. It is submitted therefore that claim 72 is patentable over the Kimpton *et al.* publication.

New claims 73 and 74, and claims 51 through 54 inclusive, as amended, are dependent claims which depend upon new claim 72 directly or indirectly, and consequently incorporate the limitations of new claim 72 by reference. For the reasons discussed above in connection with new claim 72, it is submitted that the Kimpton *et al.* publication would have neither disclosed nor in any way suggested the subject matter of new claims 73 and 74, and claims 51 through 54

inclusive, as amended. It is submitted therefore that each of new claims 73 and 74 and claims 51 through 54 inclusive as amended is patentable over the Kimpton *et al.* publication and that the rejection of claims 51 through 54 inclusive under 35 U.S.C. § 102(a) as unpatentable over the Kimpton *et al.* publication is without justification and should be withdrawn.

Claim 69 of the subject application is an independent claim directed to a method of determining for a plurality of samples analyzed with comparable biochemistry, a genotype and a confidence score for the genotype at a locus within genetic material. The method of claim 69 includes the step of measuring, under comparable conditions, a first reaction value for each sample which is indicative of the presence of a given allele at the locus. The method of claim 69 further includes the step of forming a data set from the reaction values and establishing initial probability distributions for the genotype of interest at the locus. The method of claim 69 further includes the step of calculating the conditional probability of each genotype of interest at the locus, by applying the first reaction value to each probability distribution in the set of probability distributions that corresponds to the first reaction value. Finally, claim 69 includes the step of determining the genotype and confidence score.

It is submitted that the method for automated DNA profiling employing multiplex amplification of short-tandem-repeat loci coupled with direct detection of amplified products on polyacronamid gels of the Kimpton *et al.* publication would have neither anticipated nor in any way rendered obvious the subject matter of claim 69 of the subject application. It is submitted

that the rejection of claim 69 under U.S.C. § 102(a) as unpatentable over the Kimpton *et al.* publication was unwarranted and should be withdrawn.

Claims 70 and 71 are dependent claims which depend upon claim 69 directly or indirectly, and consequently incorporate the limitations of claim 69 by reference. For the reasons noted above, it is submitted that the method of the Kimpton *et al.* publication neither anticipates nor in any way renders obvious the methods of dependent claims 70 and 71 of the subject application. It is submitted that the methods of claims 70 and 71 of the subject application are patentable over the Kimpton *et al.* publication, and that the rejection of claims 70 and 71 under 35 U.S.C. § 102(a) was without justification and should be withdrawn.

G. The Rejections Under 35 U.S.C. § 103

G.1 The Kimpton *et al.* Publication in View of the Clark Publication

The Clark publication disclosed a method for resolving ambiguities in sequencing on sequencing gels alleles from PCR-amplified DNA samples from diploid individuals. The method of the Clark publication involved obtaining DNA samples from a population of diploid individuals and identifying a homozygote or a single heterozygous site on the sequencing gel. According to lines 2 through 6 on page 112 of the Clark publication, a homozygote could be recognized on the sequencing gel by a lack of ambiguous sites. Once a homozygote was found, a haplotype had been identified. Two haplotypes were identified if the individual had a single heterozygous site. The method of the Clark publication involved tallying the haplotypes

identified by finding homozygotes and single heterozygous sites. As disclosed at line 7 through 12 on page 112 of the Clark publication, the method of resolving ambiguous sequences entailed determining, for each known haplotype, whether the haplotype could be made from some combination of the ambiguous sites. For each such haplotype, the complement of the haplotype was recovered as another potential haplotype. The process was continued until all haplotypes have been recovered or no new haplotype can be found.

It is submitted that the Clark publication in no way cures the infirmities of the Kimpton *et al.* publication as a reference against claims 51 through 54 inclusive and 60 through 69 inclusive of the subject application as amended. It is submitted therefore that the Kimpton *et al.* publication considered alone or in combination with the Clark publication would have neither disclosed nor suggested the method of claims 51 through 54 inclusive and 69 through 71 inclusive of the subject application as amended. Consequently, it is submitted that the rejection of claims 51 through 54 inclusive and 69 through 71 inclusive of the subject application under 35 U.S.C. § 103(a) as unpatentable over the Kimpton *et al.* publication in view of the Clark publication was without justification and should be withdrawn.

G.2 The Kimpton *et al.* Publication in View of the Clark Publication Further in View of the Goelet *et al.* '712 Published International Application

As disclosed in the abstract, the Goelet *et al.* '712 published international application disclosed a method for determining the identity of a nucleotide base at a specific position in a nucleic acid of interest and a method for determining the presence or absence of a particular nucleotide sequence in a sample of nucleic acids. The methods entailed contacting nucleic acid of interest with an oligonucleotide primer under hybridizing conditions and treating the resulting duplex, if any, with a terminator reagent under conditions permitting base paring of a complementary terminator present in the reagent and the occurrence of a template-dependent, primer extension reaction so as to incorporate the terminator at the 3' end of the primer. The identity of the terminator at the 3' end of the primer determined whether the hybridization occurred and the identity of the base complementary to the terminator.

The Kimpton *et al.* publication disclosed an automated DNA profiling method which employed three multiplex groups of particular three to five-base pair short-tandem-repeat loci which were amplified groupwise by PCR and analyzed by denaturing polyacrylamide sequencing gels.

It is submitted that a person of ordinary skill in the art as of the effective filing date of the subject application would not have attempted to combine the methods of the Kimpton *et al.* publication and the Clark publication with a method of the Goelet *et al.* '712 published

international application as hypothetically proposed in the outstanding Office Action, particularly since the Kimpton *et al.* publication disclosed that the method of the publication was satisfactory for its intended purpose.

It is submitted therefore that the Kimpton *et al.* publication considered alone or in view of the Clark publication or further in view of the Goelet *et al.* '712 published international application would have neither disclosed nor suggested the method of any of claims 51 through 54 inclusive and 56 through 69 inclusive of the subject application as amended and that the rejection of such claims under 35 U.S.C. § 103(a) as unpatentable over the Kimpton *et al.* publication in view of the Clark publication and further in view of the Goelet *et al.* '712 published international application should be withdrawn.

G.3 The Kimpton *et al.* Publication in View of the Clark Publication Further in View of the Backman *et al.* '663 Patent

The Backman *et al.* '663 patent disclosed a ligase chain reaction with a certain endonuclease correction and contamination control. The Backman *et al.* '663 patent does not appear to cure the infirmities of the Kimpton *et al.* publication and the Clark publication -- separately or in hypothetical combination as proposed in the outstanding Office Action -- as references against claims 51 through 54 inclusive, 56, 58, and 60 through 69 inclusive of the subject application as amended. It is submitted that the Kimpton *et al.* publication, the Clark publication, and the Backman *et al.* '663 patent considered alone or in any combination do not disclose or in any way suggest the method of claims 51 through 54 inclusive, 56, 58, and 60

through 69 inclusive and that the rejection of claims 51 through 54 inclusive, 56, 58, and 60 through 69 inclusive as amended under 35 U.S.C. § 103(a) as unpatentable over the Kimpton *et al.* publication in view of the Clark publication and further in view of the Backman *et al.* '663 patent was not justified and should be withdrawn.

H. Conclusion

For the reasons set forth above, it is submitted that the claims of the subject application as amended meet the standards of 35 U.S.C. § 112, first and second paragraphs, and are patentable over the art of record considered alone or in any combination. Early allowance of the application is therefore earnestly solicited.

Respectfully submitted,

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